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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/751,671	12/28/2000	David A. Zarling	A-68767-1/RFT/RMS/BTC	9120

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EXAMINER	
FORMAN, BETTY J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/751,671	ZARLING ET AL.	
	Examiner	Art Unit	
	BJ Forman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *1-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8 March 2004 has been entered.

Status of the Claims

2. This action is in response to papers filed 8 March 2004 in which the specification was and the previous rejections were traversed.

The amendments have been thoroughly reviewed and entered. The previous rejections in the Office Action dated 8 July 2003, reiterated below are maintained.

Applicant's arguments have been thoroughly reviewed and are discussed below.

Claims 1-8 are withdrawn.

Claims 9-16 are under prosecution.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radding et al (U.S. Patent No. 4,888,274, issued 19 December 1989) in view of Drmanac et al (U.S. Patent No. 6,383,742 B1, filed 15 August 1997).

Regarding Claim 9, Radding et al teach a method of detecting a target sequence comprising providing capture probes coated with a recombinase, contacting the target with the probe for form an assay complex and detecting the assay complex to detect the target sequence (Column 2, lines 26-64). Radding et al teach the method wherein the complex is immobilized (Column 2,lines 45-52) but they do not teach a substrate with the capture probes. However, substrates comprising capture probes where well known and routinely practiced at the time the claimed invention was made as taught by Drmanac et al who teach a similar method of probe/recombinase/target complex detection (Column 9, lines 16-45) wherein that immobilized capture probes provides for simultaneous analysis of large samples sets and parallel scoring of thousands of samples (Column 6, lines 17-27). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the capture probes of Radding et al by providing the probes on a substrate as taught by Drmanac et al to thereby provide for simultaneous analysis of large samples sets and parallel scoring of thousands of samples (Drmanac, et al, Column 6, lines 17-27) for the obvious benefits of detecting targets efficiently as taught by Drmanac et al (Column 2, lines 14-21).

Regarding Claim 10, Radding et al teach the method wherein the recombinase is rec A (Column 2, lines 26-34).

Regarding Claim 11, Radding et al teach the method wherein the recA is E. coli rec A (Column 7, lines 1-13).

Regarding Claim 12, Radding et al teach the method wherein the capture probe comprises recombinase (Column 2, lines 45-64).

Regarding Claim 13, Radding et al teach the method wherein the target comprises recombinase i.e. via complexing with the capture probe, the target comprises recombinase, see Fig. 1 and 2 (Column 2, lines 45-64).

Regarding Claim 14, Radding et al teach the method further comprises coating the target with recombinase i.e. via complexing with the capture probe, the target is coated with recombinase, see Fig. 1 and 2 (Column 2, lines 45-64).

Response to Arguments

5. Applicant argues that Radding does not teach providing an array of capture probes coated with recombinase. Applicant further argues that given the deficiencies of Radding and Drmanac, the rejection is improper. The arguments have been considered but are not found persuasive most especially for the reasons stated below regarding Drmanac. The fact that Radding does not teach every element of the instant claims is not disputed. However, Drmanac provide the missing elements and motivation to combine their teachings as discussed above and below.

6. Claims 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drmanac et al (U.S. Patent No. 6,383,742 B1, filed 15 August 1997) in view of Kigawa et al (WO 98/08975, published 5 March 1998).

Regarding Claim 9, Drmanac discloses a method of detecting the presence of a target sequence in a sample comprising: providing a substrate comprising an array of capture probes; contacting said target sequence with said array wherein either said capture probes or said target sequences is coated with a recombinase to form an assay complex; and detecting the presence of said assay complex as an indication of the presence of said target sequence (Column 9, lines 16-45). Drmanac further teaches that hybridization in the presence of recA permits hybridization to double-stranded target (Column 9, lines 22-26). Which clearly suggests that recA is present on the substrate even though Drmanac does not specifically state that their array of capture probes are coated with recA. However, Kigawa et al teach a similar method for detecting the presence of a target sequence by contacting a capture probe and target sequence and detecting the formed complex wherein the capture probe is coated with recombinase (page 12, lines 24-30) and they further teach that capture probes coated with recombinase promotes hybridization and facilitates targeting, enriching, detecting and/or isolation of target sequences (page 1). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to coat the capture probe of Drmanac et al with recombinase as they suggest (Column 9, lines 22-26) and as known in the art as taught by Kigawa et al for the expected benefit of promoting hybridization, and facilitating targeting, enriching, detecting and/or isolation of target sequences (Kigawa et al, page 1).

Regarding Claim 10, Drmanac discloses the method wherein the recombinase is recA (Column 9, lines 22-27).

Regarding Claim 11, Drmanac teaches the method of detecting the presence of a target sequence in a sample comprising: providing a substrate comprising an array of capture probes; contacting said target sequence with said array wherein either said capture probes or said

target sequences is coated with a recombinase to form an assay complex; and detecting the presence of said assay complex as an indication of the presence of said target sequence (Column 9, lines 16-45) but they do not specifically teach the recA is *E.coli* recA. However, *E.coli* recA was well known in the art at the time the claimed invention was made as taught by Kigawa et al who teach that *E.coli* recA is a recombinase which is bound to nucleic acid using well known techniques (page 14, lines 8-12). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the *E.coli* recA to the recA of Drmanac based on the known techniques for attaching the *E.coli* recA to nucleic acids as taught by Kigawa et al (page 14, lines 8-12) for the obvious benefits of using well known techniques e.g. confidence of success.

Regarding Claim 12, Drmanac discloses the method wherein the capture probe comprises said recombinase (Column 9, lines 16-45) i.e. the complex comprising the capture probe and target sequence comprises recA. Because the complex comprises recA, the capture probe which is a part of the complex also comprises recA.

Regarding Claim 13, Drmanac discloses the method wherein the target sequence comprises said recombinase (Column 9, lines 16-45) i.e. the complex comprising the capture probe and target sequence comprises recA. Because the complex comprises recA, the target sequence which is a part of the complex also comprises recA.

Regarding Claim 14, Drmanac discloses the method further comprises coating said target sequence with said recombinase (Column 9, lines 22-27) i.e. hybridization in the presence of recA inherently coats the target sequence with recombinase.

Regarding Claim 15, Drmanac teaches the method the target sequence is RNA (Column 23, lines 33-40).

Regarding Claim 16, Drmanac teaches the method comprising coating said target sequence with said recombinase (Column 9, lines 22-27) i.e. hybridization in the presence of

recA inherently coats the target sequence with recombinase wherein the target sequence is RNA (Column 23, lines 33-40).

Response to Arguments

7. Applicant argues that the cited references alone or in combination fail to teach or suggest the instant invention. Applicant traverses the passage of Drmanac cited by the office wherein it is taught that recA presence permits hybridization under non-denaturing conditions (Col. 9, lines 22-26) because Drmanac teaches a second embodiment wherein it states "a nucleic acid sample to be sequenced may be fragmented or otherwise treated (for example by the use of recA) to avoid hindrance to hybridization..". The argument has been considered but is not found persuasive for several reasons. First, the fact that Drmanac mention use of recA within a differing context/example, does not negate the fact that the clearly teach use of recA in the presence of immobilized probes as cited above. Second, Drmanac clearly teach hybridization of capture probes and target in the presence of recA. The teaching of Drmanac only differs from the instantly claimed method in that Drmanac does not specifically teach the instantly claimed ordering of contact between the probe, recA and target. The instant claims recite capture probe coated with recA and contacting the array with the target. In slight contrast, Drmanac teach hybridization of target to capture probe in the presence of recA (Column 9, lines 16-45). Hence, the method of Drmanac differs only slightly from the instantly claimed method which would have been obvious to one of ordinary skill in the art for the following reason. Given the hybridization of target to capture probe in the presence of recA teaching of Drmanac, one of ordinary skill in the art would have expected that due to ordinary hybridization kinetics, at least one of the recA proteins would contact (coat) at least one capture probe prior to target-probe contact. As such, it would have been obvious to one of ordinary skill in the art that Drmanac teaches or at the very least strongly suggests the invention as claimed.

Applicant argues that Kigawa does not cure the deficiencies of Drmanac because their methods are carried out in solution. The argument has been considered but is not found persuasive for the reasons stated above regarding Drmanac. Furthermore, the argument is not found persuasive because Kigawa clearly provide motivation for coating a probe with recA as instantly claimed i.e. promoting hybridization, and facilitating targeting, enriching, detecting and/or isolation of target sequences (Kigawa et al, page 1). Therefore, one of ordinary skill in the art would have been motivated to combine the teachings and suggestions of Drmanac and Kigawa to thereby provide an array of capture probes coated with recA as claimed.

Applicant further argues that Kigawa alone does not teach the instant invention. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

8. Claims 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kigawa et al (WO 98/08975, published 5 March 1998) in view of Drmanac et al (U.S. Patent No. 6,383,742 B1, filed 15 August 1997).

Regarding Claim 9, Kigawa et al teach a method of detecting the presence of a target sequence in a sample comprising: providing a substrate; contacting said target sequence with target sequences wherein either said capture probes or said target sequences is coated with a recombinase to form an assay complex; and detecting the presence of said assay complex as an indication of the presence of said target sequence (page 17, line 20-page 18, line 3 and Claim

18). Additionally, Kigawa et al provide a substrate to which the probe-target complex is captured (page 17, lines 26-27) but they do not capture prior to probe-target complex formation. Drmanac teaches a similar method comprising: providing a substrate comprising an array of capture probes; contacting said target sequence with said array wherein either said capture probes or said target sequences is coated with a recombinase to form an assay complex; and detecting the presence of said assay complex as an indication of the presence of said target sequence (Column 9, lines 16-45) wherein their array of capture probes provides for detection of thousands of targets simultaneously (Column 6, lines 17-21).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the array of capture probes of Drmanac and to array the capture probes of Kigawa et al onto a support for the benefits of detecting thousands of target sequences simultaneously as taught by Drmanac (Column 6, lines 17-21).

Alternatively, absence unexpected results, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Kigawa et al by immobilizing their capture probes onto the support prior to contact with the target sequence. One skilled in the art would have been motivated to array capture probes onto a support to thereby provide a reusable array of capture probes for the obvious benefit of economy of reusable components.

The courts have stated that wherein the process steps are known, absent unexpected results, the rearrangement of the process steps is prima facie obvious (see *In re Burhans* 154, F.2d 690, 69 USPQ 330 (CCPA 1946).

Regarding Claim 10, Kigawa et al teach the method wherein the recombinase is recA (page 17, lines 20-27 and Claim 28).

Regarding Claim 11, Kigawa et al teach the method wherein the recA is *E.coli* recA (page 14, lines 8-12 and Claim 28).

Regarding Claim 12, Kigawa et al teach the method wherein the capture probe comprises said recombinase (page 17, lines 20-24 and Claim 18).

Regarding Claim 13, Kigawa et al teach the method wherein the target sequence comprises said recombinase (page 17, lines 20-27 and Claim 18) i.e. the complex comprising the capture probe and target sequence comprises recA. Because the complex comprises recA, the target sequence which is a part of the complex also comprises recA.

Regarding Claim 14, Kigawa et al teach the method further comprises coating said target sequence with said recombinase (page 17, lines 20-24) i.e. hybridization in the presence of recA inherently coats the target sequence with recombinase.

Regarding Claim 15, Kigawa et al teach the method wherein the target sequence is RNA (page 11, lines 1-3 and Claim 18).

Regarding Claim 16, Kigawa et al teach the method wherein the RNA is coated with a recombinase (Claim 18) i.e. hybridization in the presence of recA inherently coats the target sequence with recombinase.

Response to Arguments

9. Applicant argues that the Kigawa and Drmanac references do not teach providing an array of capture probes coated with recombinase. Applicant argues the office's allegation of "economy of reusable components" is an unsupported allegation and thus the office has not provided valid motivation for combining the teachings. The argument has been considered but is not found persuasive because, as stated above, Drmanac clearly provide motivation to array capture probe and has provide support for that motivation i.e. to thereby detect thousands of target sequences simultaneously as taught by Drmanac (Column 6, lines 17-21).

Applicant further argues that the citation of *In re Burnhans* in inappropriate in this instance because, in contrast to the rearrangement of steps in *In re Burnhans*, the instant method is not a mere arrangement of known process steps because none of the cited references teach the instantly claimed first step i.e. providing an array of capture probes coated with

recombinase. The argument has been considered but is not found persuasive because the instant claims are drawn to a first step of providing a substrate comprising an array of capture probes coated with recombination. While the first step is recited as a single step, the single step requires assembly of the array, capture probes and recombinase. As stated above, Kigawa teach combination immobilization of capture probes, target and recombinase (page 17, line 20-page 18, line 3 and Claim 18). While they do not teach the instantly claimed ordering of those steps, i.e. providing a substrate comprising capture probes coated with recombinase and then contacting the array with the target, they clearly teach the steps of recombinase coating, hybridizing and immobilizing. Therefore, the instantly claimed method steps are known steps, but merely taught in a differing order from that of Kigawa.

10. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.129(a) and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.129(a). Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the submission under 37 CFR 1.129(a). See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741. The examiner can normally be reached on 6:00 TO 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BJ Forman, Ph.D.
Primary Examiner
Art Unit: 1634
May 7, 2004